Answer 1:

Bibliographic Information

Conditional expression of exogenous Bcl-XS triggers apoptosis in human melanoma cells in vitro and delays growth of melanoma xenografts. Hossini, Amir M.; Eberle, Jurgen; Fecker, Lothar F.; Orfanos, Constantin E.; Geilen, Christoph C. Department of Dermatology, Charite - Universitatsmedizin Berlin, Berlin, Germany. FEBS Letters (2003), 553(3), 250-256. Publisher: Elsevier Science B.V., CODEN: FEBLAL ISSN: 0014-5793. Journal written in English. CAN 139:332622 AN 2003:828951 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The Bcl-2-related proteins Bcl-XL and Bcl-XS represent alternative splice products and exert opposite activities in the control of apoptosis, but their significance for melanoma is not yet clear. Applying the tetracycline-inducible expression system Tet-On, we found overexpression of Bcl-XS by itself sufficient to induce apoptosis in vitro in stably transfected human melanoma cell lines. Combination with proapoptotic agents such as etoposide, pamidronate, and ceramide resulted in additive proapoptotic effects, whereas Bcl-XL protected from apoptosis caused via CD95/Fas stimulation. In nude mice growth of melanoma xenotransplants derived from stably transfected cells was significantly reduced after induction of Bcl-XS by doxycycline. Our results indicate that Bcl-X proteins are of major importance for control of apoptosis in malignant melanoma.

Answer 2:

Bibliographic Information

The bisphosphonate olpadronate inhibits skeletal prostate cancer progression in a green fluorescent protein nude mouse model. Yang Meng; Burton Doug W; Geller Jack; Hillegonds Darren J; Hastings Randolph H; Deftos Leonard J; Hoffman Robert M AntiCancer, Inc., San Diego, CA 92111, USA Clinical cancer research : an official journal of the American Association for Cancer Research (2006), 12(8), 2602-6. Journal code: 9502500. ISSN:1078-0432. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.) written in English. PubMed ID 16638872 AN 2006231006 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PURPOSE: Metastatic bone disease is one of the major causes of morbidity and mortality in prostate cancer patients. Bisphosphonates are currently used to inhibit bone resorption and reduce tumor-induced skeletal complications. More effective bisphosphonates would enhance their clinical value. EXPERIMENTAL DESIGN: We tested several bisphosphonates in a green fluorescent protein (GFP)-expressing human prostate cancer nude mouse model. The in vivo effects of four bisphosphonates, including pamidronate, etidronic acid, and olpadronate, on bone tumor burden in mice intratibially inoculated with PC-3-GFP human prostate cancer cells were visualized by whole-body fluorescence imaging and X-ray. RESULTS: The PC-3-GFP cells produced extensive bone lesions when injected into the tibia of immunocompromised mice. The skeletal progression of the PC-3-GFP cell growth was monitored by GFP fluorescence and the bone destruction was evaluated by X-ray. We showed that 3,3-dimethylaminopropane-1-hydroxy-1,1-diphosphonic acid (olpadronate) was the most effective bisphosphonate treatment in reducing tumor burden as assessed by GFP imaging and radiography. The GFP tumor area and X-ray score significantly correlated. Reduced tumor growth in the bone was accompanied by reduced serum calcium, parathyroid hormone-related protein, and osteoprotegerin. CONCLUSIONS: The serum calcium, parathyroid hormone-related protein, and osteoprotegerin levels were significantly correlated with GFP area and X-ray scores. Treatment with olpadronate reduced tumor growth in the bone measured by GFP and X-ray imaging procedures. Imaging of GFP expression enables monitoring of tumor growth in the bone and the GFP results complement the X-ray assessment of bone disease. The data in this report suggest that olpadronate has potential as an effective inhibitor of the skeletal progression of clinical prostate cancer.

Answer 3:

Bibliographic Information

The third-generation bisphosphonate zoledronate synergistically augments the anti-Ph+ leukemia activity of imatinib mesylate. Kuroda Junya; Kimura Shinya; Segawa Hidekazu; Kobayashi Yutaka; Yoshikawa Toshikazu; Urasaki Yoshimasa; Ueda Takanori; Enjo Fumio; Tokuda Harukuni; Ottmann Oliver G; Maekawa Taira Department of Transfusion Medicine and Cell Therapy, Kyoto University Hospital, 54 Kawahara-cho Shogoin, Sakyo-ku, Kyoto 606-8507, Japan Blood (2003), 102(6), 2229-35. Journal code: 7603509. ISSN:0006-4971. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 12763930 AN 2003420361 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Imatinib mesylate, a competitive inhibitor of Abl tyrosine kinase, is highly effective for the early stages of chronic myelogenous leukemia (CML), but remissions induced in advanced-phase CML and Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia tend to be relatively short-lived. Therefore, the search for agents that enhance the anti-Ph+ effect of imatinib mesylate is warranted. We investigated the combined effects of imatinib mesylate and the third-generation bisphosphonate zoledronate (ZOL) on Ph+ leukemias, because ZOL inhibited the prenylation of Ras-related proteins downstream of Bcr/Abl. First, we identified the potency of ZOL in vitro against human leukemic cell lines, including 2 Ph+ and a P-glycoprotein-overexpressing leukemic cell line. ZOL was also effective in vivo because as it prolonged the survival of nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice who were given xenografts with Ph+ BV173 leukemic cells. Next, we showed the in vitro synergistic effects with ZOL and imatinib mesylate for Ph+ cell lines. ZOL combined with imatinib mesylate showed synergistic effects in vivo that prolonged the survival of mice inoculated with BV173. ZOL only minimally inhibited the growth of normal hematopoietic progenitors in vitro, and mice receiving ZOL or imatinib mesylate or both tolerated these treatments well. These findings indicate that ZOL is a potent antileukemic agent that augments synergistically the anti-Ph+ leukemia activity of imatinib mesylate.

Answer 4:

Bibliographic Information

Myeloma interacts with the bone marrow microenvironment to induce osteoclastogenesis and is dependent on osteoclast activity. Yaccoby Shmuel; Pearse Roger N; Johnson Cherie L; Barlogie Bart; Choi Yongwon; Epstein Joshua Myeloma and Transplantation Research Center, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA British journal of haematology (2002), 116(2), 278-90. Journal code: 0372544. ISSN:0007-1048. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 11841428 AN 2002127193 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Myeloma tumour growth, except in the most advanced stages of the disease, is restricted to the bone marrow. We used the severe combined immunodeficient-human (SCID-hu) host system, in which primary human myeloma cells grow in, disseminate to and interact with a human microenvironment, to study the interactions between myeloma cells and cells in the bone marrow microenvironment. We used inhibitors of osteoclast activity to determine the role of osteoclasts and their products in supporting myeloma cell growth. Treatment of myelomatous SCID-hu hosts with an inhibitor of osteoclast activity (pamidronate or zoledronate) or with a specific inhibitor of the receptor activator of NF-kappaB ligand (RANKL) halted myeloma-induced bone resorption, when present, and resulted in inhibition of myeloma cell growth and survival. In contrast, myeloma cells from patients with extramedullary disease had a different growth pattern in the SCID-hu hosts and were not inhibited by these interventions, indicating that, while still dependent on a human microenvironment, these cells no longer required the bone marrow microenvironment for survival. This study demonstrates the dependence of myeloma cells on osteoclast activity and their products, and highlights the importance of the myeloma-osteoclast-myeloma loop for sustaining the disease process. Breaking this loop may help control

myeloma.